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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,459	11/12/2003	Eilon Barnea	26884	8318

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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
05/07/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/705,459	BARNEA ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37 and 72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37, 72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/20/08 has been entered.

Applicant's amendment filed 10/20/08 is acknowledged and has been entered.

Claims 37 and 72 are presently being examined.

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 37 and 72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to use the instant invention, a peptide that is SEQ ID NO: 20, including wherein SEQ ID NO: 20 "being specifically expressed in ovarian cancer cell line UCI-107."

The specification has not enabled the breadth of the claimed invention because the claims encompass: a peptide that is SEQ ID NO: 20, a peptide that may not be immunogenic *in vitro* or *in vivo*, including in the latter instance for treatment, and which may not be a marker for ovarian cancer. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the recited peptide can produce a therapeutic endpoint or is a marker for ovarian cancer. The specification discloses no working examples with regards to the *in vivo* administration of the said peptide, nor that the peptide is capable of stimulating CTL *in vitro*. The disclosed use of the peptide or of a pharmaceutical composition comprising SEQ ID NO: 20 is to treat cancer, either by *in vitro* stimulation of CTL for adoptive therapy or *in vivo* administration, respectively (page 27 at lines 4-6, Tables 8 and 9, page 114 at lines 19-30), or to study the peptide for its significance as a cancer antigen (page 54 at lines 22-25). However with regard to the latter, while the specification presents a working example of the peptide being present on one HLA-A2-expressing ovarian cancer cell

line, the working example also discloses that it is not present on another HLA-A2-expressing ovarian cancer cell line, as discussed below.

The specification discloses that peptide SEQ ID NO: 20 was detected on an HLA-A2 positive ovarian cancer cell line UCI-107, that it is a subsequence of testis-cancer antigen MAGE-B2 tumor- associated antigen and that a synthetic version of the said peptide can reconstitute HLA-A2 on the surface of RMA-S-HHD cells ([1276] and [0050]). However, the specification also discloses that peptide SEQ ID NO: 20 was not detected on a second HLA-A2 positive ovarian cancer cell line UCI-101 (Table 9 spanning pages 58-59). The specification does not disclose that SEQ ID NO: 20 is capable of stimulating CTL *in vitro* or of inducing an immune response *in vivo*. The specification discloses that "Once tumor specific MHC bound peptides are identified and their ability to stimulate an immune response is demonstrated, such peptides become candidates for adoptive immunotherapy…The potential usefulness of identified immunogenic peptides should be evaluated by the presence of specific T cells directed against them in patients inflicted with the particular cancer using standard assays such as ELISPOT and CTL. The assay of immunizing mice with the peptides described herein was meant to serve first as validation that these peptides are indeed MHC bound peptides with affinity for the HLA-A2.1 and as the preliminary indication of their immunogenic potential" (page 114 at lines 19-30). However, SEQ ID NO: 20 was not one of the peptides so assayed (especially Figure 5d, Figure 6, and [1276] of the US 20050053918 A1 publication of the instant specification).

Evidentiary reference Chaux *et al* (J. Immunol. 1999, 163: 2928-2936, of record) teach varying results between peptides used *in vivo* in different clinical trials, injection of a HLA-A1 binding MAGE-A3 peptide correlated with tumor regression in about one third of patients, dendritic cells loaded with to other HLA-A1 binding peptides yielded only a partial response in one patient, and dendritic cells pulsed with two other HLA-A2 binding peptides produced no tumor regression. Chaux *et al* teach that it is necessary to monitor CTL responses of patients to provide information on the immunogenicity of various MAGE-A1 peptide, and that the immunogenicity of the peptides may vary in different individuals (especially Discussion section).

Evidentiary reference Marchand *et al* (Int. J. Cancer 80: 219-230, 1999, of record) teach "Considerable further progress is needed, however, before immunization with tumor-specific antigens recognized by T cells becomes an effective and generally applicable cancer therapy" (second to last sentence of article).

Evidentiary reference Bodey *et al* (Anticancer Research 20: 2665-2676, 2000, of record) teach "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy (page 2665 at column 2). Bodey *et al* further teach "the use of active specific immunotherapy for cancer is still in its infancy despite several decades of clinical and basic research" (page 2668 at column 2).

Evidentiary reference Gao *et al* (J. Immunother. 23: 643-653, 2000, of record) found that although anti-tumor CTL response was enhanced by immunization, the tumors failed to regress due to an association with lack of CTL migration to the tumor sites (abstract). Thus, Gao *et al* teach that activation of peptide epitope-specific CTL is not an appropriate endpoint, and an estimation of efficacy based upon this factor is not predictive of actual efficacy of treatment *in vivo*.

Evidentiary reference Marchand *et al* (Exp. Opin. Biol. Ther. 1(3): 497-510, 2001, of record) teach "It is fair to say that in patients vaccinated with defined antigen, the immune responses induced have been so far very poor, if present. In some studies, immune responses were reported for some patients but without any correlation with the clinical responses. In addition, some patients with complete and long-term regressions of several melanoma metastases failed to mount a detectable response against the antigen present in the vaccine" (last paragraph at column 2 on page 505).

Evidentiary reference Berger *et al* (Int. J. Cancer. 111: 229-237, 2004, of record) teach "Since strong CTL responses as observed in this patient are the goal of cancer vaccination but are so far only rarely observed, the thorough analysis of patients exhibiting either exceptional clinical and/or immunologic response appears critical to understanding how vaccine therapies work and can be further improved." (abstract). Berger *et al* further teach "immune therapy for tumor patients aims at harnessing the immune system to fight cancer. Indeed, clinical trials have already shown that tumor-specific T cells can be induced even in advanced cancer patients. The induction of tumor-specific T cells, however, is not necessarily associated with a clinical response. A major obstacle in evaluating the success of a cell-based immunotherapy lies in the fact that systemic immune responses detected in the blood may not reflect the actual situation in the tumor." (column 1, page 229). Berger *et al* teach "...tumor-reactive T-cell clones persisted for prolonged time in circulation but failed to infiltrate the analyzed tumor lesions. A possible explanation for this discrepancy is provided by the recent report from a transgenic mouse model that tumors may develop an intrinisic resistance to leukocyte infiltration and effector function that prevents even persistently high levels of activated tumor-specific T lymphocytes from eradicating the tumor" (paragraph spanning columns 1-2 on page 236).

Evidentiary reference Celis (J. Clin. Invest. 2002, 110(12: 1765-1768, of record) teaches that "Unfortunately, the advantages that peptide vaccines have to offer are to some extent diminished by their inherent lack of immunogenicity, which so far has been reflected by their not-so-spectacular results in the clinic. Because the immune system in most species has evolved through time to fight life threatening infectious agents (and perhaps tumors), it should not be surprising that vaccines consisting of aseptic, endotoxin-free peptides are likely to be ignored and will likely be ineffective at inducing T cell immunity. In addition, peptides that are injected in aqueous solutions will be unsuccessful at stimulating CTL responses, either because of their rapid biodegradation

(e.g., by proteases) or, worse, because of the induction of T cell tolerance/anergy, which results from the antigenic stimulation of CTLs by non-professional APCs." Celis further teaches that an additional complication resulting from the use of synthetic peptide-derived vaccines is the induction of low affinity CTLs, that while capable of killing target cells that are exogenously pulsed with peptide, are not able to recognize the target cells that naturally process and present the peptide epitope, such as malignant cells. These low quality CTLs would have little effect in fighting and controlling disease (especially page 1765 through the paragraph spanning pages 1765-1766.

Thus, even ***if*** there were factual evidence that patients with ovarian cancer or any other cancer or pathological condition could produce a peptide-specific immune response to the SEQ ID NO: 20 peptide, there is no factual evidence that the patient's condition would clinically improve, *i.e.,* be 'treated'. Based upon the teachings of the evidentiary references cited herein, it is evident that eliciting an immune response is not sufficient to evoke a clinically significant or specific anti-tumor effect. In addition, the presence of peptide SEQ ID NO: 20 on one ovarian cancer cell line, but not another, does not establish the peptide as an ovarian cancer marker.

Since SEQ ID NO: 20 has not been demonstrated to be immunogenic, nor has it been demonstrated to be a marker for ovarian cancer, it is unpredictable whether the peptide could be used for the disclosed purposes, *i.e.,* with regard to the latter point, since peptide SEQ ID NO: 20 has only been demonstrated on one ovarian cancer cell line, while not being present on another ovarian cancer cell line, it is unpredictable that the said peptide could be used as a marker for ovarian cancer.

Therefore, because of the demonstrated unpredictability in the art of cancer immunotherapy, in the absence of sufficient exemplification and guidance, one skilled in the art cannot make and/or use the pharmaceutical composition comprising the peptide with a reasonable expectation of success. Undue experimentation would be required of one skilled in the art to practice the instant invention. See *In re Wands* 8 USPQ2d 1400 (CAFC 1988).

Applicant's arguments have been fully considered but are not persuasive.

Applicant's said arguments are of record on pages 4-5 of Applicant's amendment filed 10/20/08, briefly, that the present invention is enabled at least for research purposes in general and for cancer research in particular: (1) the peptide is derived from a known tumor antigen MAGE-B2 and has been validated as being MHC bound, (2) the peptide was detected in a particular ovarian cancer cell line UCI-107 and not in other cell lines, and (3) the specification on page 54 at lines 22-25 states that the peptides are useful in themselves for research purposes alone since study of MHC bound peptides whether immunogenic or not is of interest in general and to cancer research in particular.

However, although the peptide SEQ ID NO: 20 (p1091) is derived from MAGE-B2 and binds HLA-A2, the peptide is present on one HLA-A2-expressing ovarian cancer cell line, but not another HLA-A2-expressing ovarian cancer cell line, and the cited disclosure on page 54 concerns peptides that originate from putative tumor antigens that were recovered from solubilized HLA-A2 previously expressed on a cell line, *i.e.,* the peptides were chemically synthesized to further evaluate the accuracy of the sequencing of the biological peptides eluted from the solubilized HLA-A2, to enable their study as MHC bound peptides and their significance as cancer antigens. The further study involved detecting SEQ ID NO: 20 on one ovarian cancer cell line UCI-107, but not on another ovarian cancer cell line, nor on other cells lines (paragraph panning pages 57-58 and Table 9). Since the claimed peptide has not been demonstrated to be a marker in ovarian cancer, it is unpredictable that the claimed peptide can be used for research purposes.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 72 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 72 is indefinite in the recitation of "SEQ ID NO: 20 being specifically expressed in an ovarian cancer cell line UCI-107" because it is not clear what is meant, *i.e.,* the claim recites "as isolated peptide as set forth in SEQ ID NO: 20". Thus, it is not clear what is meant, if the peptide is isolated or cell surface expressed.

6. SEQ ID NO: 20 appears to be free of the prior art.

7. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Eileen B. O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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April 13, 2009

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